E4 Contd

least one skin conditioning agent; about 5.0 to about 15.0 wt.% of propylene glycol; and the balance in water; and

applying said lotion to said skin condition.

22. (Amended) The method of Claim 21, wherein said skin condition is selected from the group consisting of corticosteroid-responsive dermatosis, atopic dermatitis, inflammation, eczema, erythema, papulation, scaling, erosion, oozing, crusting and pruritis.

23. (Amended) The method of Claim 21, wherein said topical lotion has a 2-hour mean blanching score of at least about 2.1 and an average mean blanching of at least about 1.5.

Please add new Claims 25-27 as follows:

E5

25. (New) The topical lotion of Claim 1, wherein said lotion has a 2-hour mean blanching score of at least about 2.1 and an average mean blanching of at least about 1.5.

26. (New) The topical lotion of Claim 2, wherein said lotion has a 2-hour mean blanching score of at least about 2.1 and an average mean blanching of at least about 1.5.

27. (New) The topical lotion of Claim 13, wherein said lotion has a 2-hour mean blanching score of at least about 2.1 and an average mean blanching of at least about 1.5.

REMARKS

As indicated above, Applicants have amended the claims as follows: (1) Claims 14-18, 20 and 24 have been cancelled, (2) Claims 1-7, 9, 19 and 21-23 have been amended, and (3) Claims 25-27 have been added. Thus, upon entry of this amendment, Claims 1-13, 19, 21-23, and 25-27 are pending. Applicants respectfully submit that the noted amendments (and new claims) merely make explicit that which was (and is) disclosed or implicit in the original disclosure. No new matter is added. Attached hereto is a marked-up version of the changes made to the claims by the current amendments. The attached page is captioned "**Version With Markings To Show Changes Made.**"

1. Rejection under 35 U.S.C. § 112

Claims 20 and 24 stand rejected under 35 U.S.C. § 112, second paragraph, as being "indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention." The Examiner stated "[t]he expression 'therapeutically stable' in claims 20 and 24 is a relative term which renders the claim indefinite. The expression 'therapeutically stable' is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree." Claims 20 and 24 have been cancelled.

2. Rejection under 35 U.S.C. § 103(a)

The claims stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hill (WO 92/14472) and Gordon (Clinical therapeutics, 1998; 20(1): 26-39) in view of Richards (U.S. Patent No. 4,985,418) and Budavari (Merck Index 11th ed. 1989, monograph 6021 and 7879).

Although the Examiner recognized that "[t]he references do not expressly teach the composition as free of mineral oil and white soft paraffin", the Examiner contended:

> One of ordinary skill in the art would have been motivated to formulate a topical fluticasone composition, as free of mineral oil and white soft paraffin, with the excipient ingredients in the amount herein. Possessing the teachings of the Gordon, one of ordinary skill in the art would be reasonably expected to successfully formulate any corticosteroid topical composition such as fluticasone cream as free of mineral oil and white soft paraffin.

Applicants respectfully traverse the rejection.

The Examiner bears the initial burden of producing a *prima facie* case of obviousness. MPEP 2142. The three requirements for a *prima facie* case of obviousness are: (1) "some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings"; (2) "a reasonable expectation of success"; and (3) "the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP 2142. Applicants respectfully submit that the Examiner has failed to produce a *prima facie* case of obviousness against the claimed invention because there is no suggestion or motivation to modify or combine the reference teachings.

As set forth above, independent Claims 1 and 2 have been amended to provide for a fluticasone based topical lotion wherein the lotion comprises "up to about 5.0 wt.% of an occlusive agent selected from the group consisting of mineral oil and white soft paraffin." Claims 12 and 13, which depend from Claims 1 and 2 respectively, provide for a fluticasone

based topical lotion devoid of mineral oil and white soft paraffin. Claim 21, the only other independent claim, provides a method of treating a skin condition wherein a fluticasone based topical lotion devoid of mineral oil and white soft paraffin is provided and applied to the skin. Thus all of the claims are limited to lotions wherein the amount of mineral oil and white soft paraffin, if present, is "up to about 5.0 wt.%."

Turning to the cited art, the Examiner cites two primary references, Hill and Gordon, and two secondary references, Richards and Budavari. Regarding Hill, the Examiner contends:

> Hill teaches a topical composition employing 0.05% of the corticosteroid, fluticasone propionate, 10.00% of cetostearyl alcohol, 10% of White Soft Paraffin, 2.50 of Polysorbate 60, 10.00% of propylene glycol, and purified water (see particularly Example 1). Hill also teaches that the topical composition is prepared by mixing the ingredients and melting the mixture and then cool the mixture down (See particularly page 2, third paragraph). Hill also teaches that the topical composition is useful in treating skin conditions including inflammation (See particularly page 1, 6th paragraph).

Hill discloses pharmaceutical compositions comprising both fluticasone propionate and oxiconazole as active ingredients. In contrast to the present invention, Hill is not directed to the problem of providing lotions comprising fluticasone or a pharmaceutically acceptable salt or ester thereof that have improved vasoconstricter potency and improved organoleptic feel. Rather, Hill teaches the skilled artisan that the "combination of fluticasone propionate and oxiconazole is effective in the treatment of skin disorders wherein inflammation and infection by bacteria and/or fungi coexist." In addition, while Hill does state that the compositions disclosed therein may take the form of a lotion, creams and ointments are the preferred forms (page 2, line 8).

As the Examiner points out, Example 1 of Hill provides a composition containing 0.05% of fluticasone propionate, 10.0% of cetostearyl alcohol, 10.0% of white soft paraffin, 10.0% of propylene glycol, and purified water. It is not stated whether the composition of Example 1 is even in the form of a lotion. It may be some other form such as a cream or ointment, which is more likely given that creams and ointments are preferred and this is the only example provided. Moreover, the composition contains 10.0% of white soft paraffin, whereas Applicant's claims are limited to compositions comprising "up to about 5 wt. % of an occlusive agent selected from the group consisting of mineral oil and white soft paraffin."

Hill provides no suggestion to reduce the amount of white soft paraffin in the formulation. In fact, there is no discussion regarding white soft paraffin or other occlusive agents anywhere in Hill. Hill also provides no suggestion to prepare fluticasone-based lotions that have improved vasoconstricter potency and improved organoleptic feel. Furthermore, even though Hill states that the compositions may take the form of lotions, it directs the skilled artisan away from lotions to creams and ointments by stating that creams and ointments are preferred (page 2, line 8). Thus, Applicants find nothing in Hill that motivates the skilled artisan to prepare lotions comprising fluticasone or a pharmaceutically acceptable salt or ester thereof and "up to about 5.0 wt.% of an occlusive agent selected from the group consisting of mineral oil and white soft paraffin."

Regarding Gordon, the Examiner states:

> Gordon teaches a corticosteroid containing composition, free of mineral oil and white soft paraffin, employing Cetostearyl alcohol, cetomacrogol 1000, Isopropyl myristate, propylene glycol, Dimethicone 360, citric acid, sodium citrate, imidurea, and water (see page 28, table 1).

Gordon examines an emollient cream formulation comprising clobetasol propionate and reviews recent studies showing it is efficacious and well tolerated in treating psoriasis and atopic dermatitis. Gordon concludes that "[i]n its emollient formulation, clobetasol propionate may help soothe dry skin associated with various dermatologic conditions and contribute to improved clinical results." (page 37, column 1).

The emollient cream formulation examined in Gordon, which is described in Table I, is free of both mineral oil and white soft paraffin. Gordon does not disclose the amounts of the emollient cream formulation ingredients other than the clobetasol propionate which is 0.05%. Cetostearyl alcohol (a C_{14}-C_{20} fatty alcohol), isopropyl myristate (a skin conditioning agent), propylene glycol, and water are present in the formulation, but no amounts are given for these ingredients (Table I on page 28).

Applicants find no suggestion in Gordon that the specific formulation examined therein would be desirable or even suitable for any other topical corticosteroid, such as fluticasone propionate which has its own set of physical-chemical properties to consider in preparing formulations thereof. Applicants, accordingly, find no motivation in Gordon to substitute fluticasone or a pharmaceutically acceptable salt or ester thereof into the formulation examined therein.

Even if one did substitute fluticasone or a pharmaceutically acceptable salt or ester thereof into the Gordon formulation, Gordon provides no teaching regarding the amount of C_{14}-C_{20} fatty alcohol (cetostearyl alcohol), skin conditioning agent (isopropyl myristate), or propylene glycol. Gordon provides the skilled artisan with no suggestion to select any amounts of these ingredients (cetostearyl alcohol, isopropyl myristate, and propylene glycol), let alone Applicants' claimed amounts. Applicants, accordingly, find no motivation in Gordon to select the amount of C_{14}-C_{20} fatty alcohol, skin conditioning agent, and propylene glycol claimed.

Example 1 of Hill contains cetostearyl alcohol and propylene glycol, and the amounts present (10.0% each) are within the amounts claimed by Applicants. However, Applicants find no motivation in either Hill or Gordon to combine the teachings therein. Furthermore, Hill contains no isopropyl myristate, nor does Hill contain any discussion regarding isopropyl myristate or skin conditioning agents in general. Thus, Applicants find no motivation in Hill to select any amount of isopropyl myristate when preparing any coticosteroid based topical formulation.

As stated above, the emollient cream formulation examined in Gordon is free of both mineral oil and white soft paraffin. Gordon does not state that this feature (free of mineral oil and white soft paraffin) is necessary, required, or even desirable in the emollient cream formulation, nor does Gordon state that this feature contributes, even in part, to the results observed with the formulation. Gordon simply discloses an emollient cream formulation comprising clobetasol propionate that happens to be free of mineral oil and white soft paraffin, but provides no teaching regarding this feature. Thus, Applicants find no suggestion or motivation in Gordon to limit or eliminate the amount of mineral oil or white soft paraffin for any purpose, let alone to improve vasoconstricter potency and organoleptic feel. Likewise, Applicants find no suggestion or motivation in Gordon to apply this feature (free of mineral oil and white soft paraffin) to other topical formulations such as lotions, or to other topical formulations containing other corticosteroids.

Not only does Gordon fail to motivate the skilled artisan to limit or eliminate the amount of mineral oil or white soft paraffin when preparing fluticasone based topical formulations, the reference teaches the skilled artisan that the benefits seen with the addition of an emollient are due, at least in part, to the occlusiveness of the emollient. Gordon states "[a]n emollient added to a steroid, although not itself an active ingredient, can help restore the normal moisturizing process of the skin; this may be particularly important in soothing the

discomfort of the dry skin conditions often encountered in moderate-to-severe dermatoses." (page 26, column 1). In reviewing the rationale for combining clobetasol with an emollient, Gordon states "the effectiveness of an emollient increases with its degree of occlusiveness." (page 30, column 2). Gordon goes on to state that "[m]ore occlusive vehicles increase hydration and therefore enhance penetration of steroids through the skin. The moisturizing, hemectant, and occlusive components of an emollient cream may thus enhance penetration by improving hydration." (page 32, column 2).

These statements, which are consistent with statements made in the Background of Applicants' specification at page 1, lines 18-20, teach the skilled artisan that the presence of an emollient in the formulation examined therein contributes to the overall efficacy seen with the formulation and that this is due, at least in part, to the occlusiveness of the emollient. In light of this, Applicants find no suggestion or motivation in Gordon to limit or eliminate the amount of mineral oil and white soft paraffin, known occlusive agents, in preparing other formulations containing other topical steroids.

Thus, upon review of the Examiner's two primary references, Hill and Gordon, Applicants assert that in order to arrive at the claimed invention, the skilled artisan would have to do one of the following: (1) reduce the amount of white soft paraffin present in Example 1 of Hill from 10.0% to 5.0% or less, or (2) substitute fluticasone or a pharmaceutically acceptable salt or ester thereof for clobetasol propionate in the formulation examined in Gordon *and* select the claimed amounts of cetostearyl alcohol, isopropyl myristate, and propylene glycol.

As laid out above, neither reference provides the motivation or suggestion to reduce the amount of white soft paraffin present in Example 1 of Hill from 10.0% to 5.0% or less. Neither reference provides the motivation or suggestion to substitute fluticasone or a pharmaceutically acceptable salt or ester thereof for clobetasol propionate in the formulation examined in Gordon, and neither reference provides the motivation or suggestion to select the claimed amounts of cetostearyl alcohol, isopropyl myristate, and propylene glycol. **Thus, neither reference provides the requisite motivation or suggestion to combine or modify the references in a way that arrives at Applicants' claimed invention.**

Turning to the secondary references cited by the Examiner, Applicants assert that neither Richards nor Budavari cure the defects of Hill and Gordon. Richards is directed to "oral, stomal, or rectal" formulations comprising fluticasone propionate (column 2, lines 66-68) not topical formulations. The formulations are useful in treating inflammatory bowel

disease. Example B in column 5, lines 20-30, which the Examiner refers to in the Office Action, discloses a suspension for oral administration, not a topical formulation. The formulation does not contain a C_{14}-C_{20} fatty alcohol, skin conditioning agent, or propylene glycol. Budavari simply provides a description of methylparaben and propylparaben. No formulations containing corticosteroids are disclosed therein.

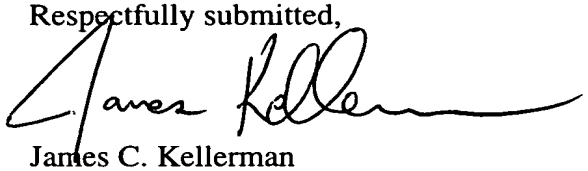
As pointed out above, all of Applicants' claims are limited to lotions comprising fluticasone or a pharmaceutically acceptable salt or ester thereof wherein the amount of mineral oil and white soft paraffin, if present, is "up to about 5.0 wt.%." There is no discussion in either Richards or Budavari regarding occlusive agents in general, or regarding mineral oil or white soft paraffin specifically. Thus, Applicants find no suggestion or motivation in Richards or Budavari to prepare a topical lotion comprising fluticasone or a pharmaceutically acceptable salt or ester thereof with a C_{14}-C_{20} fatty alcohol, skin conditioning agent, and propylene glycol in the amounts claimed, and "up to about 5.0 wt.% of an occlusive agent selected from the group consisting of mineral oil and white soft paraffin."

In conclusion, Applicants assert again that in order to arrive at the claimed invention, the skilled artisan would have to do one of the following: (1) reduce the amount of white soft paraffin present in Example 1 of Hill from 10.0% to 5.0% or less, or (2) substitute fluticasone or a pharmaceutically acceptable salt or ester thereof for clobetasol propionate in the formulation examined in Gordon *and* select the claimed amounts of cetostearyl alcohol, isopropyl myristate, and propylene glycol. Applicants find no teaching in any of the four cited references for selecting only particular features of each and combining them along the lines of the present invention. It is impermissible to first ascertain factually what the Applicants have done and then view the prior art in such a manner as to select from the random facts of that art only those which may be modified and then utilized to reconstruct the claimed invention. *In re Shuman*, 150 USPQ 54, 57 (CCPA 1966). Thus the combination of

Serial No.: 09/830,037
Group Art Unit No.: 1617

Hill, Gordon, Richards, and Budavari does not render obvious the claimed compositions. Applicants respectfully submit that the rejection has been overcome and that the claims are in condition for allowance. Reconsideration is respectfully requested.

Respectfully submitted,



James C. Kellerman
Attorney for Applicant
Registration No. 43,708

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-5929
Facsimile (610)270-5090
\\umwsfshr03\sa199900028\JCK\Cases\PU3556\amend1.doc

Serial No.: 09/830,037
Group Art Unit No.: 1617

Version With Markings to Show Changes Made

1. (Amended) A topical lotion, comprising:

about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof;

about 1.0 to 10.0 wt.% of a C_{14}–C_{20} fatty alcohol or mixtures thereof;

about 1.0 to 5.0 wt.% of at least one first skin conditioning agent;

about 5.0 to 15.0 wt.% propylene glycol;

up to about [10.0] 5 wt.% of an occlusive agent selected from the group consisting of mineral oil [or] and white soft paraffin; and

the balance in water.

2. (Amended) A topical lotion, comprising:

about 0.005 to 1.0 wt.% fluticasone propionate;

about 3.0 to 7.0 wt.% of a C_{14}-C_{20} fatty alcohol, or mixtures thereof;

about 0.5 to 3.0 wt.% of at least one first skin conditioning agent;

about 0.25 to 2.0 wt.% of at least one surfactant;

about 7.0 to 12.0 wt.% propylene glycol;

up to about [10.0] 5 wt.% of an occlusive agent selected from the group consisting of mineral oil [or] and white soft paraffin; and

the balance in water.

3. (Amended) The lotion [according to claim] of Claim 1, further comprising [less than] up to about 5.0 wt.% dimethicone.

4. (Amended) The lotion [according to claim] of Claim 2, further comprising [less than] up to about 5.0 wt.% dimethicone.

5. (Amended) The lotion [according to claim] of Claim 1, wherein said pharmaceutically acceptable ester of fluticasone [is] comprises fluticasone propionate.

6. (Amended) The lotion [according to claim] of Claim 1, comprising:

about 0.05 wt.% fluticasone propionate[,];

about 5.0 wt.% cetostearyl alcohol[,];
about 1.0 wt.% isopropyl myristate[,];
about 1.0 wt.% dimethicone[,];
about 1.0 wt.% cetomacrogol[,];
about 10.0 wt.% propylene glycol[,];
less than about 0.30 wt.% imidurea[,];
less than about 0.20 wt.% methyl paraben[,];
less than about 0.10 wt.% propyl paraben[,];
[about 0.0-5 wt.% citric acid (anyhydrous),
about 0.08 wt.% sodium citrate, and]
a preservative effective amount of imidurea, methyl paraben, and propyl paraben;
a buffering effective amount of anhydrous citric acid and sodium citrate; and
the balance in purified water.

7. (Amended) The lotion [according to claim] of Claim 1, comprising:
about 0.05 wt.% fluticasone propionate[,];
about 5.25 wt.% cetostearyl alcohol[,];
about 2.0 wt.% isopropyl myristate[,];
about 10.0 wt.% propylene glycol[,];
about 0.20 wt.% imidurea[,];
about 0.20 wt.% methyl paraben[,];
about 0.10 wt.% propyl paraben[,]; and
the balance in purified water.

9. (Amended) The lotion [according to claim] of Claim 2, [having the formula] comprising:
about 5.25 wt.% cetostearyl alcohol[,];
about 2.0 wt.% isopropyl myristate[,];
about 10.0 wt.% propylene glycol[,];
about 0.20 wt.% imidurea[,];
about 0.20 wt.% methyl paraben[,];
about 0.10 wt.% propyl paraben[,]; and
the balance in purified water.

19. (Amended) The topical lotion of [claim 18] Claim 12, wherein [the] said lotion has a 2-hour mean blanching score of at least about 2.1[, an AUC of at least about 26.7] and an average mean blanching of at least about 1.5.

21. (Amended) A method of treating a skin condition, comprising the steps of:

providing a topical lotion, [including] said topical lotion comprising about 0.005 to about 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to about 10.0 wt.% of a C_{14}-C_{20} fatty alcohol or mixtures thereof; about 1.0 to about 5.0 wt.% of at least one skin conditioning [agents] agent; about 5.0 to about 15.0 wt.% of propylene glycol; [less than about 10.0 wt.% of mineral oil or white soft paraffin,] and the balance in water; and[,]

applying [the] said lotion to [the skin having the] said skin condition.

22. (Amended) The method of [claim] Claim 21, wherein [the] said skin condition is selected from the group consisting of corticosteroid-responsive dermatosis, atopic dermatitis, inflammation, eczema, erythema, papulation, scaling, erosion, oozing, crusting [or] and pruritis.

23. (Amended) The [topical lotion] method of [claim] Claim 21, wherein [the] said topical lotion has a 2-hour mean blanching score of at least about 2.1[, an AUC of at least about 26.7] and an average mean blanching of at least about 1.5.

Please add new Claims 25-27 as follows:

25. (New) The topical lotion of Claim 1, wherein said lotion has a 2-hour mean blanching score of at least about 2.1 and an average mean blanching of at least about 1.5.

26. (New) The topical lotion of Claim 2, wherein said lotion has a 2-hour mean blanching score of at least about 2.1 and an average mean blanching of at least about 1.5.

27. (New) The topical lotion of Claim 13, wherein said lotion has a 2-hour mean blanching score of at least about 2.1 and an average mean blanching of at least about 1.5.